The Rejection of Claim 27 Under U.S.C. § 112, First Paragraph

Claim 27 is rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. Applicants respectfully traverse.

Claim 27 depends from claim 25. Claim 25 is directed to a method of screening compounds to identify as candidate agents those which have anti-cancer activity. A cell which has a genetic alteration which dysregulates *c-MYC* expression is contacted with a test compound. The genetic alteration causes *c-MYC* overexpression. CDK4 kinase activity of the cell is measured. A test compound which inhibits the CDK4 kinase activity is identified as a candidate agent with anti-cancer activity. Claim 27 specifies that the cell is a neuroblastoma cell.

To comply with the written description requirement, the description must clearly convey to persons of ordinary skill in the art that applicants invented what is claimed. *In re Gosteli*, 872 F.2d 1008, 1012 (Fed. Cir. 1989). The specification meets this requirement.

The Office Action, however, asserts that the claims are not described because "[t]he specification does not teach whether a neuroblastoma cell has a genetic alteration which dysregulates c-MYC." Office Action at page 3, lines 4-5. The Office Action cites Maris *et al.* (*J. Clin. Oncol.* (1999) *17*:2264-2279) as teaching "that neuroblastoma is remarkably heterogeneous and MycN is amplified in neuroblastoma, not c-MYC." Office Action at page 3, lines 6-8.

The specification teaches that neuroblastoma cells may indeed have a genetic alteration which dysregulates *c-MYC*. The specification discloses, "Preferably the tumor cell will have a genetic alteration which causes c-MYC overexpression. Such alterations are known to occur in Burkitt's Lymphoma, neuroblastoma, and colon cancer." Page 8, lines 11-13. Thus, the

specification conveys to those of skill in the art that applicants had possession of the concept of using neuroblastoma cells comprising a genetic alteration that causes *c-MYC* overexpression.

Furthermore, before the effective filing date of the application, February 12, 2000, it was known in the art that many neuroblastomas overexpress *c-MYC*. Xiaoning *et al.* teaches that "there was a high expression rate of c-myc oncogene in these [neuroblastoma] cases by *in situ* hybridization and immunocytochemical methods. Along with the result of N-myc expression, we believe that the two oncogenes may contribute to the tumorigenesis of neuroblastoma." (*Chinese Medical Sciences Journal* (1999) *14*:102-106; Exhibit A) Page 105, column 2, lines 11-16. Thus, neuroblastomas with *c-MYC* dysregulation were known in the art.

The teachings of the specification and the state of the art at the time the application was filed, clearly demonstrate that applicants had possession of a method to screen compounds to identify candidate agents with anti-cancer activity using a neuroblastoma cell comprising a genetic alteration that dysregulates *c-MYC* expression.

Applicants respectfully request withdrawal of the rejection.[1]

The Rejection of Claims 25, 26, and 28-32 Under 35 U.S.C. § 103(a)

Claims 25, 26, and 28-32 are rejected under 35 U.S.C. § 103(a) as unpatentable over Gura (*Science* (1997) *278*:1041-1042), Dang (*Mol. Cel. Biol.* (1999) *19*:1-11), and Musgrove (*Mol. Cel. Biol.* (1998) *18*:1812-1825). Applicants respectfully traverse.

[1] The Office Action concludes the rejection by stating that "[i]t is the Office's position that screening a large quantity of clinical samples require undue experimentation. Considering the limited guidance, no working examples, the quantity of experiments involved, it is concluded that undue experimentation is required." Page 3, lines 9-12. This statement appears to relate to an enablement, and not a written description, rejection. Nonetheless, applicants urge that in view of the teachings in the specification and in Xiaoning *et al.*, cited above, one of skill in the art would readily have been able to use neuroblastoma cells that have a genetic alteration which dysregulates *c-MYC* expression in the claimed screening methods. Xiaoning *et al.* teach that 80-85% of the neuroblastomas they screened had dysregulated *c-myc*. See abstract. At such a high rate of occurrence a large quantity of screening would not be required.

As indicated above, the claims are directed to methods of screening compounds to identify as candidate agents those which have anti-cancer activity. The methods employ a cell which has a genetic alteration which dysregulates *c-MYC* expression. Candidate agents are identified as those which inhibit CDK4 kinase activity of the cell.

The U.S. Patent and Trademark Office bears the initial burden of establishing a *prima facie* case of obviousness. The *prima facie* case requires three showings:

> First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.

Manual of Patent Examining Procedure, 8th ed., § 2142.

"When determining the patentability of a claimed invention which combines two known elements, 'the question is whether there is something in the prior art as a whole to suggest the desirability, and thus the obviousness, of making the combination.'" *Ecolochem, Inc v. Southern California Edison Co.* 227 F.3d 1361, 1372 (Fed. Cir. 2000).

The Office Action has not made a *prima facie* case of obviousness because there is no suggestion or motivation in the references or in the art to combine the reference teachings. One of ordinary skill in the art would not have been motivated to combine the teachings of Gura, Musgrove, and Dang to arrive at the claimed method of screening compounds to identify candidate agents having anti-cancer activity.

The Office Action cites Gura as teaching that the future of cancer drug screening may be through the use of molecular targets. Office Action at page 4, lines 12-14. The Office Action cites Musgrove as teaching an anti-cancer drug that inhibits CDK4 in *in vitro* cancer cells and

concludes that Musgrove "fairly suggest[s] that CDK4 could be a molecular target since the drug [which] inhibited CDK4 is already used for breast and endometrial cancers." Office Action at page 5, lines 1-3. The Office Action cites Dang as suggesting that therapeutic insight might emerge by focusing on the c-myc protein in cancer biology and as teaching that c-myc and CDK4 are involved in cell cycle regulation. Office Action at page 5, lines 12-14. The Office Action asserts that

> it would have been prima facie obvious to one having ordinary skill in the art at the time the claimed invention was made to screen candidate anti-cancer drugs using CDK4 and c-myc as molecular targets with reasonable expectation of success because Musgrove et al., teach that a clinically relevant anti-cancer agent inhibits CDK4 and Dang teaches that c-myc is dys-regulated in many cancers. One of ordinary skill is motivated to screen anti-cancer [drugs] using a molecular target because Gura teaches the other methods had not been working very well and suggests a screening method using a molecular target.

Office Action at page 5, lines 15-22. Even if, *arguendo*, the references actually teach the asserted facts, none of the references teaches or suggest using a cell with an alteration which dysregulates *c-MYC* expression to screen for CDK4 inhibitory agents. One would have to pick and choose among the teachings of the prior art to select the particular elements of the subject claims and combine them in the manner recited. But such selective picking and choosing is not proper and certainly does not evidence a suggestion or teaching to combine.

Gura teaches that methods of screening for potential anticancer drugs, *e.g.*, xenograft and knockout mouse models, often do not predict molecules that will perform well against human cancers *in vivo*. See page 1041 column 2, line 29 to column 3, line 58. Gura further teaches that it may be possible to screen potential anticancer agents by targeting specific genetic defects. Gura teaches, "'the future of cancer drug screening is turning almost exclusively toward defining

molecular targets.' If the approach works, drug developers would finally have an easy way to identify promising cancer drugs." Page 1042, column 3, lines 56-61. Gura teaches some genetic defects that have been used to generate mouse models to screen anticancer compounds. These targets include *APC* (page 1041, column 3, line 45), *RB* (page 1041, column 3, line 61), *BRCA1* (page 1041, column 3, line 65), and *p21* (page 1042, column 2, lines 13-14). Gura, however, does not teach or suggest using a genetic alteration which dysregulates *c-MYC* expression for use in a cell-based screening assay. Likewise, Gura does not teach or suggest that *c-MYC* directly regulates CDK4 expression and so can be used to amplify a CDK4 assay signal. Thus, Gura does not teach or suggest measuring CDK4 kinase activity of a cell having a genetic alteration that dysregulates *c-MYC* expression.

Musgrove and Dang would not have motivated one of ordinary skill in the art to modify Gura's teaching to measure CDK4 kinase activity in cells having a genetic alteration that dysregulates *c-MYC* expression. Musgrove teaches the mechanism by which synthetic progestin decreases CDK4 and CDK2 activity in T-47D breast cancer cells. Thus, Musgrove teaches contacting cells with an agent that inhibits CDK4 activity. However, Musgrove does not teach or suggest that the T-47D cells have a genetic alteration that dysregulates *c-MYC* expression.

Moreover, Musgrove provides no suggestion to substitute cells which have a genetic alteration which dysregulates *c-MYC* expression for the T-47D breast cancer cells. The Office Action points to Musgrove's teaching that the "role of c-myc and CDKs in cell cycle control has been studied." Office Action at page 4, line 21 to page 5, line 1. The mere fact that Musgrove teaches that c-MYC and CDKs are involved in cell cycle control would not have motivated one of ordinary skill in the art to contact cells having a genetic alteration that dysregulates c-MYC expression and to measure CDK4 kinase activity of those cells.

Moreover, Musgrove teaches that decreased CDK4 activity in the progestin-treated T-47D tumor cell line is not linked to *c-MYC* expression levels. Musgrove tested the effect of *c-MYC* and *Cdc25A*[2] expression on CDK4 activity following progestin treatment of T-47D cells. Musgrove determined that *c-MYC* and *Cdc25A* expression levels decrease in response to progestin treatment. Musgrove teaches, "The decrease in *c-myc* expression was apparent within 6 h, thus preceding the decline in Cdc25A expression by >12 h." Page 1817, column 2, lines 8-10. Musgrove then determined whether the decreased *c-MYC* and *Cdc25A* expression levels were linked to the decrease in CDK4 activity. To make this determination, Musgrove added bacterially expressed and purified cdc25A to immunoprecipitated CDK4 complexes from progestin-contacted cells and tested whether adding cdc25A to the complexes restored CDK4 kinase activity. See page 1817, column 2, lines 13-17. Musgrove found that the "experiments failed to demonstrate Cdc25A activation of Cdk4 immunoprecipitates from either control or progestin-treated cells, despite 15-fold increases in the amount of added Cdc25A (Fig. 7C)." Page 1817, column 2, lines 39-42. Musgrove urges that "[t]hese data argue against decreased Cdc25A expression contributing to the decrease in Cdk4 activity following progestin treatment." Page 1817, column 2, line 42 to page 1818, column 1, line 1. The decreased *Cdc25A* expression results from decreased *c-MYC* expression.[3] Thus, Musgrove teaches that there is no relationship between decreased *c-MYC* expression and decreased CDK4 activity in progestin-treated T-47D cells. Thus, Musgrove would not have motivated one of ordinary skill in the art to screen

[2] Musgrove teaches, "Of the family of phosphatases responsible for relieving this inhibition [of CDK4], Cdc25A appears to have specificity for G1 CDKs in vivo, and therefore its expression was examined. . . . In view of evidence for c-myc regulation of Cdc25A, *c-myc* expression was also examined." Page 1817, column 1, line 32 to column 2, line 5.

[3] Musgrove teaches, "In view of evidence for c-myc regulation of Cdc25A, *c-myc* expression was also examined." Page 1817, column 2, lines 4-5.

compounds for their effect on CDK4 activity in cells which have a genetic alteration which dysregulates *c-MYC* expression.

Dang teaches that *c-MYC* is activated in human and animal tumors. Dang also reviews c-MYC target genes and the roles of c-MYC in cell biology. Dang's Table 1 lists thirty-one different putative c-MYC target genes. Dang does not list CDK4. Dang teaches that one of the roles played by *c-MYC* in cell biology is as a regulator of cell cycle progression. Dang also teaches that the relationship between c-MYC and CDK4 via cdc25A has not been established:

> More recently, evidence has been provided that the *cdc25A* gene is a direct target of c-Myc. The connection between c-Myc and *cdc25A* has not been confirmed in other studies, indicating that differences in experimental models might account for the discrepancy. This gene [cdc25A] produces a protein phosphatase that activates both CDK2 and CDK4.

Page 5, column 2, lines 34-39, emphasis added. Thus, there was no confirmed relationship between c-myc and CDK4, even an indirect one.

Dang, like Musgrove, provides no teaching or suggestion that would have motivated one of ordinary skill in the art to screen compounds using cells which have a genetic alteration which dysregulates *c-MYC* expression by measuring CDK4 activity of the cells for any reason.

The combination of Gura, Musgrove, and Dang would not have motivated one of ordinary skill in the art to selectively combine elements of their teachings t achieve the claimed invention. The combination fails to teach or suggest the use of cells that have a genetic alteration that dysregulates c-MYC expression in a method of screening compounds for candidate agents that have anti-cancer activity by measuring the ability of the compound to inhibit CDK4 activity of those cells. Thus the *prima facie* case of obviousness must fail.

Applicants respectfully request withdrawal of this rejection to claim 25, and dependent claims 26 and 28-32.

Respectfully submitted,

Date: August 6, 2004

By: _____
Michelle Holmes-Son
Registration No. 47,660